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An updated review
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Title page

Medical treatment and comorbidity in polycystic ovary syndrome— an updated review

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Abstract

Polycystic ovary syndrome (PCOS) is defined by hyperandrogenism, irregular menses and polycystic ovaries when other etiologies are excluded. The risk of type 2 diabetes and cardiovascular disease is increased in PCOS. Furthermore, the immune function in PCOS is impaired with elevated circulating of autoantibodies and increased risk of thyroid disease. Especially obese women with PCOS are at increased risk of non-alcoholic fatty liver disease.

Medical treatment of PCOS involves antiandrogen treatment in combination with insulin sensitising drugs. Oral contraceptives are often applied as anti-androgens, but spironolactone could have additional vascular benefits. New and upcoming treatments for PCOS involve GLP-1 agonists, DPP4 inhibitors, SGLT2 inhibitors, myoinositol, thyroid hormones, and vitamin supplements. Statins are rarely indicated for treatment of dyslipidemia in PCOS, but statins could improve PCOS phenotype. Use of antidepressants in PCOS could have adverse effects on PCOS metabolic phenotype.

In the present article we give an update regarding established and upcoming medical treatment for PCOS and for comorbidities of PCOS.
Introduction

The pathogenesis of PCOS involves central obesity, insulin resistance, low grade inflammation, and hyperandrogenism. Women with PCOS have increased risk of cardio-metabolic diseases including a 3 times increased risk for type 2 diabetes [1]. Lifestyle intervention is considered the cornerstone of treatment for PCOS [2]. However, additional medical treatment is often needed and most commonly involves antiandrogen treatment in combination with insulin sensitizing treatment. Table 1 gives a list of the most commonly applied treatments in PCOS. New and upcoming insulin sensitizers in PCOS include GLP-1 agonists, DDP4 inhibitors, and SGLT2 inhibitors. Recent studies supported that statin treatment could decrease hyperandrogenism and improve insulin sensitivity in PCOS. Myoinositol and vitamin D could be new “over the counter” drugs for treatment of PCOS.

Recent publications documented that the risk of non-alcoholic fatty liver disease, thyroid diseases, and depression was increased in PCOS [3-6]. The optimal treatment for comorbid conditions in PCOS is debated. Furthermore, treatment with for example antidepressants could affect the metabolic phenotype of PCOS.

The aim of the present review was to give an updated overview regarding medical treatment of PCOS including PCOS related comorbidities. We focused on published studies within the last two years. Based on available data, we discuss the indication for medical treatment in PCOS and how medical treatment can affect PCOS phenotype.

Methods

We searched for articles published from January 2017 until September 2019 in PubMed. We searched for available meta-analyses and clinical trials in study cohorts with PCOS. We also searched for papers including each identified treatment modality: Oral contraceptives, spironolactone, metformin, GLP-1 agonist, SGLT2 inhibitor, DPP4 inhibitor, pioglitazone, rosiglitazone, PPARgamma, myoinositol, statin, thyroid hormone, D-vitamin in combination with the search term PCOS. Further relevant studies were identified by cross search from reference lists in identified studies. We excluded studies regarding fertility treatment, pregnancy, and pregnancy outcomes. Treatment of hirsutism is covered in another chapter, and local treatment for hirsutism
is not included. Lifestyle intervention is considered outside the scope of the chapter and is covered only briefly.

Antiandrogen treatment in PCOS

Treatment with oral contraceptive pill (OCP) regulates menstrual cycles and SHBG levels are increased, leading to decreased levels of free testosterone and decreased hirsutism scores. OCP is widely applied in PCOS. More than 50% Danish women with PCOS had prescriptions of OCP compared to 25% controls [3]. Second generation OCPs have the lowest thromboembolic risk and is considered first choice, however, 4th generation OCPs containing drospirenone may be superior regarding antiandrogen effects [7, 8]. Due to thromboembolic risk, OCP containing 35 ug ethinyl estradiol and 2mg spironolactone should only be used in severe cases of hirsutism and acne if other OCPs fail in treatment outcome [9]. Furthermore, limited amount of data exist regarding OCPs containing estradiol or estradiol valerate, but the contraindications for these OCPs are similar to that of ethinylestradiol containing OCP. The effect of OCP on long term health in PCOS is debated and still awaits long term studies. In population based studies in PCOS, use of OCP was an independent predictor of development of type 2 diabetes, cardiovascular disease and autoimmune disease [4, 5, 10]. Increased insulin levels during OGTT in women with PCOS treated with OCP [11] along with weight gain [12] could increase the risk of development of CVD. Furthermore, OCP therapy was associated with activation of the coagulation system [13] and increased thromboembolic risk [14]. Therefore, the possible benefits of OCP on PCOS-related symptoms should be balanced against possible metabolic side effects in each patient.

Spironolactone only: Spironolactone is a non-selective mineralocorticoid receptor antagonist, and suppresses levels of testosterone. The antiandrogen effects of spironolactone are comparable to OCP regarding treatment of hirsutism [15], but spironolactone could have additional benefits regarding risk of CVD as discussed below. Furthermore, combining spironolactone with metformin was superior to monotherapy with either drug regarding improved menstrual cycles, glucose during oral glucose tolerance test (OGTT), assessed by area under the curve (AUC) and testosterone levels [16]. Treatment with spironolactone in young women
with PCOS is, however, complicated by the need for safe birth control, and the drug will be, primarily, indicated outside the reproductive age.

Metabolic syndrome, diabetes, and non-alcoholic fatty liver disease (NAFLD) in PCOS

The metabolic syndrome in women is defined as waist circumference ≥ 88 cm, impaired glucose tolerance, blood pressure >130/85 mmHg, high density lipoprotein (HDL) <1.3 mmol/l, and triglyceride (TG) >1.7 mmol/l [17]. Overall, 50% of women with PCOS fulfill the criteria of the metabolic syndrome [3, 17]. Type 2 diabetes was diagnosed in 1.5-10% women with PCOS [3, 5, 18], and a recent meta-analysis reported an odds ratio of 2.9 for type 2 diabetes in women with PCOS compared to weight matched controls [19].

Prediabetes is defined as glucose levels in the grey zone above normal levels and below diabetes thresholds. In the general population, up to 70% individuals with prediabetes will develop diabetes [20]. Impaired glucose tolerance was found in 10-36% women with PCOS, which corresponded to an odds ratio of 3.2 compared with controls [19]. Approximately 75% of women with PCOS are overweight or obese and in prospective studies, obesity was the most important predictor of deteriorated glucose tolerance in PCOS [17, 21-23]. Less than 1% normal weight women with PCOS had type 2 diabetes during OGTT [5, 18].

NAFLD: The metabolic syndrome and particularly type 2 diabetes is associated with increased risk of nonalcoholic fatty liver disease (NAFLD). NAFLD may progress from simple steatosis to alcoholic steatohepatitis, liver fibrosis, cirrhosis, and eventually hepatocellular carcinoma [24]. Hepatic overexpression of SHBG was associated with decreased fat hepatic lipogenesis in a mouse model [25]. The risk of NAFLD was 3 times increased in women with PCOS [26, 27]. Androgen excess and low SHBG predicted development of NAFLD in PCOS [26, 27]. Circulating liver enzymes is the easiest way to assess liver cell damage, but the sensitivity and specificity are low. Measurement of liver enzymes upon PCOS diagnosis could be relevant at least in obese and overweight women, but the need for continuous awareness of NAFLD remains to be determined. Treatment with antidiabetics could decrease the risk of NAFLD [28], and is discussed further below. Therapeutic increase in SHBG levels, for example with OCP, could protect against NAFLD [25, 29].

The close association between obesity and metabolic risk in PCOS underline the importance of life style
intervention as first line treatment [2, 30]. Unfortunately, lifestyle modification is rarely associated with lasting weight loss [31]. Appetite regulation is impaired in PCOS and adherence to lifestyle modification programs may therefore be more difficult in PCOS compared to controls.

**Bariatric surgery.** In Denmark, women with PCOS combined with infertility can be referred for bariatric surgery if BMI > 35 kg/m² if other treatments have failed. A recent meta-analysis reported that the average weight loss after bariatric surgery corresponded to nearly 15 kg/m² in women with PCOS [32]. Bariatric surgery was followed by improved ovulation rate, lower testosterone levels and decreased risk of type 2 diabetes [32]. Pregnancy should be avoided within two years after bariatric surgery, and long term data are needed regarding costs and benefits of bariatric surgery in women with PCOS [33].

**Insulin sensitizing treatment in PCOS**

**Metformin** is probably the most commonly prescribed insulin sensitizer in PCOS. Twelve percent Danish women with PCOS had prescriptions of metformin compared to 0.4% controls [3]. Metformin increases insulin sensitivity and improves ovulatory function in PCOS, whereas androgen levels and hirsutism scores are only mildly improved [34]. In a recent meta-analysis, the effect of metformin on weight was only modest in studies of maximum 24 weeks duration [35], whereas 12 months metformin treatment induced a median weight loss of 3 kg [12]. Metformin could have additional positive effects on quality of life [36], gallbladder movements [37], NAFLD [28], and cancer risk [38]. The possible anti-inflammatory effect of metformin is undetermined [17]. Metformin improves menstrual cycles, body composition, and vascular markers also in lean women with PCOS [12, 39]. These findings support that treatment with metformin is of benefit also in lean women with PCOS and metformin remains an important cornerstone of medical treatment in PCOS. Metformin may also be used in combination with OCP, where metformin may counteract the negative effects of OCP on glucose status.

**GLP-1 agonists** could be a promising group of insulin sensitizers in selected women with PCOS. Glucose stimulated GLP-1 secretion, during OGTT, was not impaired in women with PCOS, but GLP-1 secretion was significantly lower in obese compared to lean women with PCOS [11]. GLP-1 agonist treatment decreased BMI and testosterone and improved ovulation rate in obese women with PCOS [40, 41]. The average weight loss during 6 months GLP-1 treatment (1.8 mg/day) was 5 kg [41]. Combined GLP-1 (1.2 mg) and
metformin treatment was associated with a more moderate weight loss than high dose GLP-1 (3 mg), but had less gastrointestinal side effects [42]. GLP-1 agonist treatment is more efficient than metformin regarding weight loss and insulin sensitivity [43]. However, once GLP-1 treatment is stopped, the patient may regain weight. An average weight gain of 5 kg was reported after terminating GLP-1 (3 mg) in women with PCOS despite shifting from GLP-1 to metformin treatment [44]. Therefore, GLP-1 agonists should only be prescribed in selected populations of women with PCOS and safe birth control is needed [41]. The indication for GLP-1 treatment could be need for weight loss before fertility treatment or before bariatric surgery. High economic cost can be an additional reservation for use of GLP-1 agonists in PCOS. In Denmark, patients without diabetes have to pay full price for treatment with GLP-1 (cost corresponds to 8 Euro/day).

DPP4 inhibitors stimulate insulin secretion through decreased degradation of incretins and are considered weight neutral in patients with type 2 diabetes. Recent studies found that treatment with DPP4 inhibitors in obese women with PCOS was followed by lower blood glucose [45, 46] and weight loss [45]. Shift from GLP-1 agonist treatment to DDP4 inhibitor treatment in obese women with PCOS prohibited weight gain [44]. Growth hormone levels are reduced in women with PCOS [47]. Treatment with DPP4 inhibitor increased growth hormone half-life and inter-pulse interval, which suggested that improved growth hormone secretion could be a mechanism for decreased visceral fat mass during DPP4 treatment in PCOS [45]. At present there are limited data regarding DPP4 inhibitor treatment in PCOS, and treatment will still be considered experimental.

SGLT2 inhibitors act on the sodium-glucose-cotransporter-2 to increase urinary glucose secretion and promote weight loss and improve cardiovascular risk in patients with T2D. At present, only one study investigated the effect of treatment with SGLT2 inhibitor in PCOS (average BMI 36 kg/m²) [48]. Treatment with SGLT2 inhibitor was more efficient than metformin regarding weight loss and fat mass reduction, whereas changes in hormonal and metabolic parameters were comparable between SGLT2 inhibitor and metformin treatment [48]. More studies are needed regarding treatment with SLGT2 inhibitors in PCOS before introducing these drugs in daily clinic.

Peroxisome proliferator-activated receptor gamma (PPARγ) agonist treatment is associated with decreased peripheral adipocyte lipolysis and fat redistribution from central to peripheral fat. In PCOS,
PPARγ agonist treatment improved hormonal and metabolic outcomes, but had an adverse effect on weight
[34]. Weight gain limits the use of PPARγ agonists in PCOS. Furthermore, PPARγ agonists stimulate stem
cells in bones and leads to differentiation into adipocytes in preference of osteoblasts [49]. In accordance, bone mineral density and markers of osteoblast activity decreased in women with PCOS after PPARγ agonist
treatment [50]. Glitazones could be superior to metformin in women with severe NAFLD [28], but new data support that GLP-1 agonists represent safe and efficient treatment modalities for NAFLD [28].

Myoinositol is a food supplement and acts as insulin sensitizer. Myoinositol treatment compared to placebo improved insulin sensitivity in women with PCOS without significant effect on BMI [35, 51]. At present, myoinositol has been applied especially during fertility treatment in PCOS [52], but quality of studies varies and more data are needed [53]. Inositol treatment had less gastrointestinal side effects compared to metformin, whereas the effect on menstrual cycles, insulin, and testosterone were comparable between the two treatment modalities [54]. The place for myoinositol in PCOS treatment is still undetermined, but myoinositol could be applied when metformin treatment is not tolerated.

Cardiovascular disease in PCOS
Coronary artery calcification and echocardiographic abnormalities were more common in PCOS compared to controls and the risk of coronary heart disease and stroke in women with PCOS was two times increased [3, 4]. It is recommended that women with PCOS should be screened for the presence of the components of the metabolic syndrome by the time of diagnosis, whereas the intervals for subsequent follow up are debated [55]. Especially the need for prospective screening of lipids and blood pressure in premenopausal, lean women with PCOS needs clarification [4].

Dyslipidemia – treatment with statins in PCOS
Dyslipidemia was present in more than 70% newly diagnosed women with PCOS [3]. In register based studies, the diagnosis dyslipidemia was three times increased in patients with PCOS vs. controls [2] and the prescription rate of anti-lipids was two times higher [2, 19]. The risk of dyslipidemia in PCOS was associated with BMI [56]. Most guidelines recommend that lipids should be measured by time of diagnosis of PCOS, whereas prospective lipid measurements depend on individual risk profile [55]. The risk of
cardiovascular disease according to baseline lipid profile in PCOS has not been investigated in long term clinical studies. Therefore, the indication for treatment with anti-lipids in PCOS follows available guidelines from national and international cardiologic societies [56]. According to these guidelines, treatment with statins is indicated in women of very high or high risk for cardiovascular disease (http://www.heartscore.org/en_GB/access). Treatment with statins should be initiated in women with for example diabetes, known cardiovascular disease (including treatment for hypertension), or elevated total cholesterol >8.0 mmol/L (http://www.heartscore.org/en_GB/access). We recently investigated the implication of measuring lipid profiles in PCOS in a Nordic study population [56]. We found that measurement of lipids did not change clinical care in in young women <35 years and no risk factors for cardiovascular disease [56] and we therefore questioned the relevance of prospective lipid measurement in low risk women with PCOS [56]. Recent studies supported that statin treatment may improve PCOS related symptoms outside dyslipidemia. Statins decreased androgen levels in PCOS [57] and could have an anti-inflammatory effect [58]. Combined statin and metformin treatment was superior to mono-treatment with metformin regarding lipid profile, insulin sensitivity, and ovarian function [59, 60]. Statin treatment could however deteriorate insulin sensitivity [58] and data regarding ovarian function during statin treatment were not uniform [60]. Therefore, the indication for statin treatment in women with PCOS awaits more clinical studies.

Hypertension – antihypertensive treatment in PCOS

Hypertension was diagnosed in around 10% women with PCOS [61] and blood pressure is higher in women with PCOS compared to controls [62]. In register based studies, the diagnosis hypertension was three times increased in patients with PCOS vs. controls [3, 4, 63]. The risk of hypertension in PCOS was associated with BMI, but hypertension was also present in normal weight individuals [4, 64, 65]. The recent PCOS guideline recommends that blood pressure should be measured by the time of PCOS diagnosis and annually during follow up [55]. However, data are limited regarding treatment of hypertension in PCOS. At present, therefore, treatment of hypertension in PCOS will follow available guidelines for non-PCOS study populations. According to Danish guidelines, treatment for hypertension is indicated with persistent blood pressure > 135/90 mmHg and presence of risk factors. Risk factors include elements of the metabolic
syndrome, smoking, and first degree relatives with cardiovascular disease. Treatment for hypertension is also
indicated in persons with known cardiovascular disease. Treatment of hypertension in PCOS is complicated
by the fact that treatment should be adjusted before pregnancy. Hyperandrogenism could be a predisposing
factor for hypertension in PCOS [4]. Therefore, prescription of spironolactone could be first choice to
improve hyperandrogen symptoms, decrease blood pressure, and improve endothelial function in women
with PCOS [65]. However clinical studies are needed to test this hypothesis and reservation regarding safe
birth control could be a limitation for more widespread use of spironolactone in young women with PCOS.

Autoimmune, inflammatory, and infectious diseases in PCOS

Low grade inflammation in PCOS is associated with obesity. In obesity, the number of adipose tissue-
resident macrophages is increased in both subcutaneous and visceral adipose tissue and the circulating
mononuclear cells are more inflammatory active [66]. High testosterone levels in PCOS promote abdominal
obesity, which may induce insulin resistance [67]. Insulin resistance induces hyperinsulinemia and
subsequently stimulates the ovarian and adrenal hormonal production, inhibits sex hormone binding globulin
(SHBG) production, and thereby testosterone activity increases [67]. Increased inflammatory status,
unbalanced oestrogen/ progesterone secretion or still unknown mechanisms may impair immune function in
PCOS [68]. Women with PCOS had increased secretion of autoantibodies, which could explain increased
relative risk of rheumatologic diseases and type 1 diabetes [68], still the absolute risk of these diseases was
low [3]. Similar mechanisms were suggested to affect respiratory health and increase the risk of asthma in
PCOS [69]. The relative risk of asthma was 1.5-2.5 times increased in PCOS [69] and nearly 20% women
with PCOS had prescriptions of asthma medicine [3].

Thyroid dysfunction in PCOS and treatment with thyroid hormone: Rates of positive thyroid
autoantibodies was higher in PCOS vs. controls [70] and subclinical hypothyroidism was present in 10-25%
women with PCOS [71]. The presence of overt thyroid diseases was 3.6 times increased in PCOS vs.
controls and prescriptions of thyroid medicine were 3 times increased [3]. Overt hypothyroidism resembles a
PCOS phenotype i.e. insulin resistance, dyslipidemia, weight gain, decreased levels of SHBG, anovulatory
cycles, and infertility [72]. Women with PCOS and subclinical hypothyroidism had a more adverse metabolic
phenotype with higher waist circumference, dyslipidaemia and higher HOMA-ir levels [10, 71, 72], but high normal baseline TSH did not predict cardiovascular outcome [10, 71]. Screening for overt thyroid disease is relevant in PCOS and measurement of TSH is part of the routine evaluation program in women with clinical suspicion of PCOS. Furthermore, TSH measurement should be repeated by time of planning pregnancy and in the postpartum period [10]. The clinician should be aware of that increased awareness of thyroid disease introduces bias regarding the prevalence of (subclinical) hypothyroidism in women with PCOS. Available data do not support prescription of thyroid hormone in women with PCOS and subclinical hypothyroidism.

**Depression and antidepressants in PCOS**

The risk of depression was up to five times increased in PCOS [3, 73] and 16.9% Danish women with PCOS had prescriptions of antidepressants compared to 8.8% controls [3]. Quality of life and mental health in PCOS is covered in a separate chapter in this publication. The long term effect of antidepressive treatment on metabolic risk and PCOS phenotype has been sparely evaluated and no long term studies exist. A meta-analysis found improved glycemic control in patients with type 2 diabetes and depression treated with antidepressants [74]. We recently reported that treatment with escitalopram increased cortisol levels and waist circumference in women with PCOS and no clinical depression, whereas measures of insulin resistance were unchanged [75]. Clearly, more studies are needed to determine long term metabolic and clinical outcomes after anti-depressive treatment in women with PCOS and depression [75].

**Vitamin D and PCOS**

Vitamin D levels were lower in women with PCOS compared to controls and hypovitaminosis D may be present in more than 75% women with PCOS [76]. Vitamin D levels were inversely associated with BMI [77] and low vitamin D levels could increase the risk of autoimmune diseases in PCOS including subclinical hypothyroidism [78]. However, recommendations regarding routine measurement of vitamin D levels are inconsistent and the impact of vitamin D treatment on reproductive and cardio-metabolic risk factors in PCOS remains to be established [79]. Recent meta-analyses reported that treatment with vitamin D in PCOS
was associated with decreased HOMA-ir and glucose levels [80], decreased triglyceride levels [81] and
improved ovulatory function [82], whereas sex hormone levels were unchanged [81]. Therefore, screening
for vitamin D levels is relevant upon diagnosis of PCOS and vitamin D substitution could be relevant
especially in overweight and obese women.

Conclusion

Medical morbidity is increased in PCOS. Upon diagnosis, women with PCOS should be screened for the
metabolic syndrome and thyroid disease and measurement of D-vitamin levels and liver enzymes is
recommended in obese women with PCOS. Long term morbidity in PCOS could be affected by medical
treatment and the need for prospective screening for other medical diseases awaits future prospective studies.
Table 1. Overview of most common comorbidities in PCOS (outside pregnancy)

<table>
<thead>
<tr>
<th>Comorbidity</th>
</tr>
</thead>
<tbody>
<tr>
<td>Metabolic syndrome (waist &gt; 88 cm, impaired glucose tolerance, elevated blood pressure, dyslipidemia)</td>
</tr>
<tr>
<td>Type 2 diabetes</td>
</tr>
<tr>
<td>Cardiovascular disease including hypertension</td>
</tr>
<tr>
<td>Autoimmune diseases (thyroid disease, rheumatoid arthritis, type 1 diabetes, asthma)</td>
</tr>
<tr>
<td>Non-alcoholic fatty liver disease</td>
</tr>
<tr>
<td>Depression</td>
</tr>
<tr>
<td>Hypovitaminosis D</td>
</tr>
</tbody>
</table>
Table 2: Overview of effects of different treatment regimens of PCOS

<table>
<thead>
<tr>
<th>Treatment Modality</th>
<th>Ovulation</th>
<th>Hirsutism</th>
<th>Insulin resistance</th>
<th>BMI</th>
<th>Lipids</th>
<th>Safe during pregnancy?</th>
<th>Most common Side effects</th>
</tr>
</thead>
<tbody>
<tr>
<td>Insulin sensitizers</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Metformin</td>
<td>↑</td>
<td>→</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>Yes/?</td>
<td>Gastrointestinal (Diarrhea, vomiting, loss of appetite).</td>
</tr>
<tr>
<td>GLP-1 agonists</td>
<td>↑</td>
<td>→</td>
<td>↓</td>
<td>↓</td>
<td>↓</td>
<td>No</td>
<td>Gastrointestinal (Diarrhea, vomiting, loss of appetite).</td>
</tr>
<tr>
<td>Myoinositol</td>
<td>↑</td>
<td>→</td>
<td>↓</td>
<td>→?</td>
<td>?</td>
<td>Yes/?</td>
<td>Probably none?</td>
</tr>
<tr>
<td>Anti-androgens</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Oral contraceptive</td>
<td>→</td>
<td>↓</td>
<td>↑?</td>
<td>↑ (↑)</td>
<td>↑</td>
<td>n/a</td>
<td>Depression, oedema, mastalgia</td>
</tr>
<tr>
<td>Spironolactone</td>
<td>↑</td>
<td>↓</td>
<td>↓</td>
<td>→?</td>
<td>?</td>
<td>No</td>
<td>Mastalgia, tiredness, electrolyte derangement</td>
</tr>
<tr>
<td>Other</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>D-vitamin</td>
<td>↑</td>
<td>→</td>
<td>↓</td>
<td>→?</td>
<td>↓</td>
<td>Yes</td>
<td>None (intoxication rare)</td>
</tr>
<tr>
<td>Statins</td>
<td>↑</td>
<td>→</td>
<td>↓</td>
<td>→?</td>
<td>↓</td>
<td>No</td>
<td>Liver affection, muscle pain, cerebral</td>
</tr>
</tbody>
</table>

Possible benefits (green) and side effects (red) of different treatment modalities in PCOS

Safe during pregnancy: Can the drug be used safely in pregnancy? Yes/?: The drug should probably be stopped at positive pregnancy test.
19. Kakoly, N.S., et al., The Impact of Obesity on the Incidence of Type 2 Diabetes Among...


23. Ollila, M.E., et al., Overweight and obese but not normal weight women with PCOS are at increased risk of Type 2 diabetes mellitus-a prospective, population-based cohort study.


39. Niafar, M., et al., A systematic review of GLP-1 agonists on the metabolic syndrome in


Seyam, E. and E. Hefzy, Long-term effects of combined simvastatin and metformin treatment on the clinical abnormalities and ovulation dysfunction in single young women.


